Claims 1-17 were rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

Claim 1 has been amended by adding "to form said phosphate linkage". In view of the amendment to Claim 1, Applicants believe this aspect of the rejection is overcome.

Claim 2 has been amended by replacing "preparing" with "synthesizing". In view of the amendment to Claim 2, Applicants believe there is now sufficient antecedent basis for this limitation of the claim.

Claim 3 has been amended by replacing "irradiating" with "removing". In view of the amendment to Claim 3, Applicants believe there is now sufficient antecedent basis for the claim.

Claim 5 has been amended by substituting "P" with "PR". The structure of Claim 5 has been supported on pages 5 and 21 of the specification. Applicants believe that substituting 'P" with "PR" to clarify the claim language as recommended by the Examiner introduces no new matter.

In view of the above, Applicants respectfully request that each of the noted aspects of the rejection be withdrawn.

Rejection under 35 U.S.C. § 103 (a)

Claims 1-17 were rejected under 35 U.S.C. § 103 (a) as allegedly being unpatentable over Earhart et al. in view of McGall et al.

Earhart et al. teach a method for synthesizing desired polymers within molecular array elements by applying droplets containing a reactive monomer. One of the steps involves oxidization of a phosphite triester group to form a phosphotriester group by the addition of iodine in THF, pyridine, and water. Earhart et al. fails to disclose or suggest varying of iodine concentration and specifically do not recite wherein the concentration of iodine used in the oxidation step ranges from about 0.005 M to about 0.05 M, wherein the iodine concentration is about 0.02 M. The Examiner notes that in general, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. The Examiner asserted that Applicant's recitation of a particular

range of iodine concentration in an oxidation solution is not considered inventive since there is no evidence that the particular concentration range recited in the instant claims is critical to the claimed method. Applicants respectfully traverse this rejection.

Applicants show that the use of iodine from about 0.005 M to about 0.05 M in a mixture comprising water and solvent in the oxidation step is critical in obtaining improved functional performance of arrays as measured by signal, background and detection. Figure 2 and page 24 demonstrates the significantly enhanced functional performance of arrays synthesized under the claimed method compared to the standard method as measured by the amount detection of 1.5 pM spike probes. Figure 3 and page 24 demonstrates the significantly enhanced functional performance of arrays synthesized under the claimed method as measured by overall signal. The results are unexpected to one of skill in the art that varying concentration of iodine in the oxidation step would lead to significantly enhanced functional performance of arrays. The claimed invention is not routine experimentation as asserted by the Examiner because a particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. MPEP § 2144.05 (II)(B).

Therefore, Applicants respectfully request reconsideration and withdrawal of the noted aspect of the rejection.

McGall et al. describes the use of photo-removable protecting groups in synthesis of oligonucleotide arrays. McGall et al. do not disclose or suggest the claimed iodine concentration of the present application. For similar reasons provided above, Applicants submit that a prima facie case of obviousness has not been set forth by the Office and respectfully request that this rejection be withdrawn.

Conclusion

In view of the discussion above, Applicants' claims are patentable over the cited references. No reference, or combination of references, shows or suggests the pending claims, which are limited to methods of synthesizing a nucleic acid array on a support comprising an oxidation step with a solution of from about 0.005 M to about 0.05 M

iodine in an aqueous solvent mixture. Consequently, Applicants respectfully request that the Examiner reconsider and withdraw the rejections and pass the present application to issuance. Such action is hereby solicited.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 408-731-5875.

Please charge any fees that may be required to process this amendment to PTO Deposit Account No. 01-0431.

Respectfully submitted,

Date: 3/27/02

Man Sung Co

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Version Of Amendments With Markings To Show Changes Made

Please amend claims 1, 2, 3, and 5 as follows:

1. A method of oxidizing a phosphite ester linkage in a nucleic acid array to a phosphate linkage, comprising contacting said phosphite ester linkage with a solution of from about 0.005 M to about 0.05 M iodine in a mixture of water and organic solvent to form said phosphate linkage.

2. A method of [preparing] synthesizing a nucleic acid array on a support, wherein each nucleic acid occupies a separate known region of the support, said synthesizing comprising:

(a) activating a region of the support;

(b) attaching a nucleotide to a first region, said nucleotide having a masked reactive site linked to a protecting group;

(c) repeating steps (a) and (b) on other regions of said support whereby each of said other regions has bound thereto another nucleotide comprising a masked reactive site link to a protecting group, wherein said another nucleotide may be the same or different from that used in step (b);

(d) removing the protecting group from one of the nucleotides bound to one of the regions of the support to provide a region bearing a nucleotide having an unmasked reactive site;

(e) binding an additional nucleotide to the nucleotide with an unmasked reactive site;

(f) repeating steps (d) and (e) on regions of the support until a desired pluarlity of nucleic acids is synthesized, each nucleic acid occupying separate known regions of the support;

wherein said attaching and said binding are each made by covalently forming a phosphite triester linkage between said nucleotides and said unmasked reactive site and further comprising oxidizing said phosphite triester linkage to a phosphate triester linkage with a solution of from about 0.005 M to about 0.05 M iodine in an aqueous solvent mixture.

3. A method in accordance with claim 2, wherein said synthesizing comprises the sequential steps of:

a) removing a photoremoveable protecting group from at least a first area of a surface of a substrate, said surface comprising immobilized nucleotides on said surface, said nucleotides capped with a photoremovable protective group, without removing a photoremoveable protecting group from at least a second area of said surface;

b) simultaneously contacting said first area and said second area of said surface with a first nucleotide to couple said first nucleotide to said immobilized nucleotides in said first area, and not in said second area, said first nucleotide capped with said photoremovable protective group;

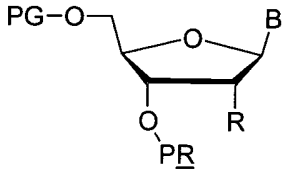
c) removing a photoremoveable protecting group from at least a part of said first area of said surface and at least a part of said second area;

d) simultaneously contacting said first area and said second area of said surface with a second nucleotide to couple said second nucleotide to said immobilized nucleotides in at least a part of said first area and at least a part of said second area;

e) performing additional [irradiating] removing and nucleotide contacting and coupling steps so that a matrix array of at least 100 nucleic acids having different sequences is formed on said support;

with the proviso that the coupling steps further comprise oxidizing an initially formed phosphite ester linkage to a phosphate ester linkage using from about 0.005 M to about 0.05 M iodine in an aqueous solvent mixture.

5. A method in accordance with claim 3, wherein said nucleotides have the formula:



wherein

B is a member selected from the group consisting of natural or unnatural adenine, natural or unnatural guanine, natural or unnatural thymine, natural or unnatural cytosine, and natural or unnatural uracil;

R is a member selected from the group consisting of hydrogen, hydroxy, protected hydroxy, halogen and alkoxy;

PR is a phosphoramidite group; and

PG is a photoremoveable protected group.